AHFS Final Determination of Medical Acceptance: Off-label Use of Palbociclib in Combination with Trastuzumab +/- Pertuzumab and Endocrine Therapy for the Treatment of Patients With HR+/HER2+ Metastatic Breast Cancer

Drug: Palbociclib

Off-label Use: HR+/HER2+ metastatic breast cancer

Off-label Use for Review:

- Results from a phase 3, randomized, open-label, international trial

Strength of Evidence: Level 1 (high strength/quality)

Grade of Recommendation: Recommended (accepted)

Narrative Summary:

An estimated 20 to 25% of all breast cancer cases are human epidermal growth factor receptor 2-positive (HER2+), with nearly 50% of these patients also hormone receptor positive (HR+).[10001] Patients with HR+/HER2+ metastatic breast cancer generally have a worse prognosis than patients with HR+/HER2- disease and are more apt to exhibit resistance to therapy.[10001] In guidelines, the basis of treatment for patients with HR+/HER2+ breast cancer is HER2-targeted therapy in combination with chemotherapy or endocrine therapy.[10001] Ongoing research is evaluating various combinations of drug regimens in this patient population including the use of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors.[10001]

The phase 3, randomized, open-label, international PATINA trial evaluated the efficacy and safety of the addition of the CDK4/6 inhibitor, palbociclib, to standard first-line maintenance therapy after induction chemotherapy in patients with histologically confirmed HR+/HER2+ metastatic breast cancer and no prior therapy.[10002] Enrolled patients had no evidence of disease progression following completion of induction therapy (i.e., 6 to 8 cycles, including trastuzumab +/- pertuzumab and taxane/vinorelbine).[10002] A total of 518 patients were randomly assigned to palbociclib 125 mg orally once daily for 21 consecutive days with trastuzumab +/- pertuzumab +

endocrine therapy or trastuzumab +/- pertuzumab + endocrine therapy alone.[10002] Trastuzumab and pertuzumab were administered per standard of care; therapeutic options for endocrine therapy included fulvestrant or an aromatase inhibitor. [10002] Therapy was administered until disease progression or intolerable toxicity.[10002] primary study endpoint was investigator-assessed progression-free survival (PFS), which was performed at a median follow-up of 53 months.[10002] The data cutoff for the final PFS analysis was October 15, 2024.[10002] The key secondary endpoint was overall survival (OS).[10002]

At baseline, the median age of patients was 53.4 years (range: 44.2 to 61.4), 99.4% were female, and the majority were White (91.7%), with 3.5% Black or African American and 2.1% Asian Indian/Chinese/other Asian.[10002] Over 97% of patients received pertuzumab and almost 90% of patients were administered an aromatase inhibitor as endocrine therapy.[10002] A complete or partial response to induction therapy occurred in 68.5% of patients by investigator assessment, with stable disease present in 31.5% of patients.[10002]

The addition of palbociclib significantly improved PFS by 26% compared with the control arm.[10002] The median PFS was 44.3 months in the palbociclib arm and 29.1 months in the control arm (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.58 to 0.94).[10002] At the time of the analysis, OS remained immature; median overall survival was not evaluable in the palbociclib arm and was 77 months in the control arm.[10002] The 5-year overall survival rates were 74.3% versus 69.8% in the palbociclib and control arms, respectively.[10002] The confirmed objective response (29.9% versus 22.2%) and clinical benefit (89.3% versus 81.3%) rates were significantly improved with the addition of palbociclib.[10002]

The most common adverse event in the palbociclib arm was grade 3 neutropenia (63.2% versus 4.4%).[10002] In addition, grade 2 and 3 fatigue, stomatitis, and diarrhea occurred more frequently in the palbociclib arm.[10002] The incidence of grade ≥4 adverse events was similar across study groups (12.3% versus 8.9% for palbociclib versus control).[10002] Discontinuation of therapy due to adverse events was reported by 14 patients in the palbociclib arm.[10002] No treatment-related deaths were reported in the study.[10002]

Based on current evidence, palbociclib in combination with trastuzumab +/- pertuzumab and endocrine therapy for the treatment of patients with HR+/HER2+ metastatic breast cancer has Level 1 (high strength/quality) evidence supporting its use.[10002] The addition of palbociclib to standard therapy in the first line metastatic setting significantly improved PFS with a manageable toxicity profile.[10002]

Dosage

For the first line treatment of HR+/HER2+ metastatic breast cancer in patients without disease progression following induction therapy, the recommended adult dosage of palbociclib is 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment.[10002] Palbociclib is administered in combination with anti-HER2 and endocrine therapy (e.g., fulvestrant or an aromatase inhibitor).[10002]

References:

10001. Ran R, Ma Y, Wang H, Yang J, Yang J. Treatment strategies for hormone receptor-positive, human epidermal growth factor receptor-2 positive (HR+/HER2+) metastatic breast cancer: a review. *Front Oncol*. 2022;12:975463.

10002. Metzger O, Mandrekar S, DeMichele A, et al. AFT-38 PATINA: a randomized, open-label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy vs anti-HER2 therapy + endocrine therapy after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer. San Antonio Breast Cancer Symposium. December 10-13, 2024.

Oncology Expert Committee Voting Results and Comments:

Vote (6 of 7 committee members returned the ballot):

Proposed Level of Evidence: Level 1 (High strength/quality)

Concur with rating: 6 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 5 respondents

Reasonable choice (Accepted, with possible conditions): 1 respondent

Not fully established (Equivocal): 0 respondent

Not recommended (Unaccepted): 0 respondent

Reviewer Comments on Level of Evidence and Grade of Recommendation

The evidence to support palbociclib in patients with HR+/HER2+ MBC is based largely from the PATINA study. The study itself has a robust design with a significant PFS improvement (over 15-month gain in PFS with palbociclib). There are some limitations which can hamper the AFHS rating, mainly its open-label design and that long-term outcomes are maturing. However, this is a regimen used frequently in clinical practice.

The addition of palbociclib to standard maintenance therapy (trastuzumab +/- pertuzumab and aromatase inhibitor or fulvestrant) for patients with HR+/HER2+ breast cancer after induction therapy without progression is a reasonable choice based on the PATINA trial data. A statistically

significant and clinically meaningful PFS of 44.3 in the intervention group compared to the control (21.9 months) was found with HR 0.74 (CI 0.58, 0.94). Five-year survival rates were marginally better in the palbociclib arm (74.3%) compared to the control (69.8%). Limitations include the lack of representative minority populations which would limit generalizability of the findings. Both groups were more likely receiving an aromatase inhibitor over fulvestrant. Although toxicities were described as manageable, Grade 3 adverse events were notably higher in the palbociclib group: severe neutropenia (grade 3): 63.2% vs. 4.4% and diarrhea (Grade 2 and 3): 26.4% and 11.1% vs. 10.5% and 1.6%. The addition of palbociclib to standard therapy in this patient population is a reasonable choice. Data on baseline performance status were not readily available, which would impact real-world decision-making. The increased toxicity burden should be weighed against benefits, considering patient preferences and quality of life.

Randomized placebo-controlled phase 3 trial with demonstrated measurable benefit in PFS. MOA logical with CDK4/6 inhibitor benefit to overcome resistance.

Final Grade of Recommendation: Accepted

Participants:

AHFS Staff Members (writing and editing): Michael Gabay PharmD, JD, BCPS

AHFS Oncology Expert Committee Members (reviewing and voting): Caroline Clark MSN, RN; Donald Moore PharmD, BCOP; Jason Bergsbaken PharmD, BCOP; Christine Gegeckas RPh, BCOP; Kirollos Hanna PharmD, BCOP; Eve Segal PharmD, BCOP; Kate Taucher PharmD, BCOP

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off- label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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